General

Guideline Title

VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care.

Bibliographic Source(s)

Management of Chronic Kidney Disease Working Group. VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 117 p. [171 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for management of chronic kidney disease in primary care. Washington (DC): Department of Veteran Affairs, Department of Defense; 2007. 126 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the Department of Veterans Affairs and the Department of Defense (VA/DoD) and the National Guideline Clearinghouse (NGC): The recommendations for the management of chronic kidney disease (CKD) in primary care are organized into 3 modules with 1 algorithm. The modules with accompanying recommendations are presented below. See the original guideline document for the algorithm and evidence tables associated with selected recommendations, including level and quality of evidence, strength of recommendation, and supporting evidence citations.

The strength of recommendation grading (Strong For, Weak For, Strong Against, Weak Against) is defined at the end of the "Major Recommendations" field.

Evaluation for CKD

1. While there is insufficient evidence to associate exposure to depleted uranium and solvents such as hydrocarbons with CKD, the guideline panel suggests that clinicians take a detailed occupational and non-occupational history. (Weak For)
2. The guideline panel suggests that periodic evaluation for CKD be considered in patients with the following:
    a. Diabetes, hypertension, other end organ disease (e.g., chronic heart failure [CHF]), or a personal or family history of kidney disease
    b. Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma)
    c. History of acute kidney injury (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis)
    d. Elderly patients

e. Races and ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)

(*Carryover modified from the 2008 CPG*) (Weak For)

Acute Kidney Injury Avoidance

Prevention of Contrast-Induced Nephropathy (CIN) in Patients with CKD

3. The guideline panel suggests that patients at increased risk for CIN receive volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following iodinated contrast administration. (Weak For)
4. The guideline panel suggests offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis. (Weak For)
5. Given inconsistent evidence, the guideline panel does not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis. (Weak For)
6. The guideline panel recommends against the use of renal replacement therapy (RRT) for CIN prophylaxis. (Strong Against)
7. The guideline panel suggests not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography. (Weak Against)
8. The guideline panel suggests not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography. (Weak Against)

Management of Chronic Kidney Disease

Self-Management Strategies

9. The guideline panel suggests the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with CKD. (Weak For)
10. In patients with stage 3 and 4 CKD, the guideline panel suggests a protein diet of 0.6 to 0.8 g/kg/day as it may slow the decline in glomerular filtration rate (GFR) and progression to end-stage renal disease (ESRD). (*Carryover modified from the 2008 CPG*) (Weak For)
11. There is insufficient evidence to recommend for or against weight loss in obese patients as an intervention to reduce proteinuria or to slow progression of CKD. However, the guideline panel suggests weight loss interventions in obese patients as part of an overall health improvement strategy. (Weak For)
12. There is insufficient evidence to recommend for or against exercise with or without lifestyle intervention to reduce ESRD, mortality, change in GFR, or change in urinary protein. However, the guideline panel suggests regular exercise as part of an overall health improvement strategy. (Weak For)
13. There is insufficient evidence to recommend for or against health education to reduce time to dialysis initiation or to reduce mortality. However, the guideline panel suggests CKD health education because it supports the aim of maximizing patient-centered care. (Weak For)
14. There is insufficient evidence to recommend smoking cessation to halt progression of CKD; however, the guideline panel suggests tobacco cessation for cardiovascular risk reduction in patients with CKD. (Weak For)

Clinical Management Strategies

15. The guideline panel suggests offering multidisciplinary care, if available, for patients with CKD to reduce non-fatal stroke, slow progression from micro- to macroalbuminuria, and reduce all-cause mortality. (Weak For)
16. Although there is insufficient evidence to recommend for or against referral to a nephrology specialist for patients with stage 3 CKD for slowing CKD progression, the guideline panel suggests consultation with a nephrologist to assist in the diagnosis and treatment of patients with any of the following conditions:
    a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant)
    b. Kidney function that is rapidly worsening without obvious cause
    c. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism)
    d. CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care
    e. Nephrotic range proteinuria
    f. Nephrolithiasis

    (Weak For)

17. The guideline panel recommends that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections:
    a. Influenza vaccine*

b. Tetanus, diphtheria, acellular pertussis (Tdap) vaccine
c. Pneumococcal polysaccharide vaccine (i.e., 13-valent pneumococcal conjugate vaccine [PCV13] and 23-valent pneumococcal polysaccharide vaccine [PPSV23])
d. Hepatitis B vaccine
e. Zoster/shingles vaccine*
f. Varicella vaccine*
g. Measles, mumps, rubella (MMR) vaccine*

*Note: Live vaccines, including nasal influenza (live attenuated influenza vaccine [LAIV]), may be contraindicated in patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents.

(*Carryover modified from the 2008 CPG*) (Strong For)

18. The guideline panel recommends that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD. (*Carryover modified from the 2008 CPG*) (Strong For)
19. In patients with CKD, the guideline panel suggests that medications should be reviewed and their dosing modified, where appropriate, according to the level of the patient's kidney function. (*Carryover modified from the 2008 CPG*) (Weak For)
20. The guideline panel suggests the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD. (Weak For)
21. In adult patients with stages 1-4 CKD, the guideline panel recommends that blood pressure targets should be less than 140/90 mmHg. (*Carryover modified from the 2008 CPG*) (Strong For)
22. In patients with non-diabetic CKD, hypertension, and albuminuria, the guideline panel recommends the use of an angiotensin-converting enzyme inhibitor (ACEI) to prevent progression of CKD. Angiotensin II receptor blockers (ARBs) may be substituted for patients with an ACEI-induced cough. (*Carryover modified from the 2008 CPG*) (Strong For)
23. In patients with diabetes, hypertension, and albuminuria, the guideline panel recommends the use of an ACEI or ARB to slow the progression of CKD, unless there is documentation of intolerance. (*Carryover modified from the 2008 CPG*) (Strong For)
24. The guideline panel recommends against the use of combination renin-angiotensin-aldosterone system (RAAS) blockade (ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor) in patients with CKD. (Strong Against)
25. The guideline panel recommends that all patients with CKD who are not on dialysis and have no known history of coronary artery disease be assessed for 10-year CVD risk using a validated risk calculator for primary prevention. If at risk (as defined in the NGC summary of the VA/DoD guideline VA/DoD clinical practice guideline for the management of dyslipidemia for cardiovascular risk reduction), the guideline panel recommends use of at least a low dose statin. (Strong For)
26. The guideline panel suggests against the use of statins prescribed with the intent of slowing eGFR decline or preserving kidney function. (Weak Against)
27. The guideline panel recommends against intensive glycemic control to patients with stage 3 or worse CKD due to the lack of benefit on renal or cardiovascular outcomes and potential for significant harm. (*Carryover modified from the 2008 CPG*) (Strong Against)
28. The guideline panel suggests initiation of oral iron therapy (in preference to parenteral) to support iron requirements in patients with CKD stages 3 and 4. (Weak For)
29. The guideline panel recommends against offering erythropoiesis-stimulating agents (ESAs) to patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension. (Strong Against)
30. The guideline panel recommends against initiating ESAs at a hemoglobin level greater than 10 g/dL. (Strong Against)
31. The guideline panel suggests offering supplemental vitamin D to correct vitamin D deficiency in patients with CKD stages 3 or 4. (Weak For)
32. The guideline panel suggests not offering active vitamin D analogs or calcitriol to patients with stage 3 and 4 CKD with elevated parathyroid hormone (PTH) levels due to lack of evidence for kidney, bone, or cardiovascular benefit and increased potential of harm from hypercalcemia. (Any use of active vitamin D analogs should be managed by a nephrologist.) (Weak Against)
33. The guideline panel suggests not offering phosphate binders to patients with stage 3 and 4 CKD with normal serum phosphorous. (*Carryover modified from the 2008 CPG*) (Weak Against)
34. The guideline panel suggests not offering calcimimetics to patients with stage 3 and 4 CKD due to lack of evidence for kidney or cardiovascular benefit and increased risk of harm from hypocalcemia. (Weak Against)

Definitions:

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

*Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*, 924-926.

Strength of Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

The grade of each recommendation is presented as part of a continuum:

- Strong For (or "The guideline panel recommends offering this option …")
- Weak For (or "The guideline panel suggests offering this option …")
- Weak Against (or "The guideline panel suggests not offering this option …")
- Strong Against (or "The guideline panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Clinical Algorithm(s)

An algorithm for the management of chronic kidney disease (CKD) in primary care is provided in the original guideline document.

Scope

Disease/Condition(s)

Chronic kidney disease (CKD)

Guideline Category

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Nephrology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of patients who are experiencing chronic kidney disease (CKD), leading to improved clinical outcomes
- To enhance clinician awareness of risk factors for CKD
- To highlight evidence-based approaches that prevent acute kidney injury, which is a contributor to the development of CKD
- To identify pharmacologic and treatment strategies that have been shown to delay the progression of CKD to end-stage renal disease

Target Population

Patients with chronic kidney disease (CKD) stages 1-4

Note: The patient population of interest for this Clinical Practice Guideline (CPG) is adults (men and women), that are eligible for care in the Veterans Health Administration (VHA) and Department of Defense (DoD) health care delivery system. It includes deployed and non-deployed Veterans as well as active duty Service Members. This CPG does not provide recommendations for the management of CKD in children or adolescents.

Interventions and Practices Considered

Evaluation/Prevention

1. Detailed occupational and non-occupational patient history
2. Periodic evaluation for chronic kidney disease (CKD) in high-risk patient groups
3. Acute kidney injury avoidance: prevention of contrast-induced nephropathy (CIN)
    - Volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate)
    - Oral hydration

Management/Treatment

Self-Management Strategies

1. Dietary sodium restriction
2. Protein diet of 0.6 to 0.8 g/kg/day in patients with stage 3-4 CKD
3. Weight loss interventions in obese patients as part of an overall health improvement strategy (insufficient evidence to recommend to reduce proteinuria or to slow progression of CKD)
4. Exercise with or without lifestyle intervention as part of an overall health improvement strategy (insufficient evidence to recommend to reduce end-stage renal disease [ESRD], mortality, change in glomerular filtration rate [GFR] or change in urinary protein)
5. CKD health education to maximize patient-centered care (insufficient evidence to recommend to reduce time to dialysis initiation or reduce mortality)
6. Smoking/tobacco cessation for cardiovascular risk reduction (insufficient evidence to recommend to halt progression of CKD)

Clinical Management Strategies

1. Multidisciplinary care
2. Referral to a nephrology specialist (if indicated)
3. Vaccinations (influenza; tetanus, diphtheria, acellular pertussis [Tdap]; pneumococcal polysaccharide; hepatitis B; zoster/shingles; varicella; measles, mumps, rubella [MMR])
4. Avoiding or limiting the use of nephrotoxic medications
5. Review of medications and dosing modifications where appropriate
6. Bicarbonate supplementation in CKD patients with metabolic acidosis
7. Establishment of blood pressure targets
8. Use of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)
9. Assessment for 10-year cardiovascular disease (CVD) risk using a validated risk calculator
10. Oral iron therapy (in preference to parenteral) to support iron requirements
11. Supplemental vitamin D (to correct deficiency in CKD stages 3 or 4)

Note: The following interventions were considered but not recommend or there was insufficient evidence to recommend:

Administration of N-acetylcysteine (NAC)
Renal replacement therapy for CIN prophylaxis
Statin therapy for CIN prophylaxis in patients undergoing elective angiography
Theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography
Combination renin-angiotensin-aldosterone system blockade (ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor)
Use of statins prescribed with the intent of slowing estimated glomerular filtration rate (eGFR) decline or preserving kidney function
Intensive glycemic control in patients with stage 3 or worse CKD
Erythropoiesis-stimulating agents (ESAs) for the purpose of achieving a hemoglobin target above 11.5 g/dL or use at a hemoglobin lever greater than 10 g/dl
Active vitamin D analogs or calcitriol in patients with stage 3 and 4 CKD with elevated parathyroid hormone
Phosphate binders in patients with stage 3 and 4 CKD with normal serum phosphorous
Calcimimetics in patients with stage 3 and 4 CKD

Major Outcomes Considered

- Disease progression, including rate of progress to end-stage renal disease (ESRD), increase in serum creatinine, proteinuria, and development of cardiovascular disease
- Patient-oriented clinical outcomes, including disease-related morbidity (e.g., stroke), treatment-related adverse events, hospitalization, quality of life, and mortality
- Development of acute kidney injury
- Degree of association of occupational exposure with acute kidney disease or chronic kidney disease (CKD)
- Change in blood markers such as vitamin D level, parathyroid hormone levels, and phosphate levels; bone density (dual-energy x-ray absorptiometry [DEXA] scans); decrease in bone fractures; and mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on chronic kidney disease (CKD). These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the Veterans Affairs (VA) and Department of Defense (DoD) populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare

Research and Quality (AHRQ). See Table A-1 in Appendix A in the original guideline document for a brief overview of the PICOTS typology.

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest.

See Appendix A in the original guideline document for information on population, interventions, and outcomes that helped form the key questions.

Conducting the Systematic Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by the AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. The methods also follow the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

Extensive literature searches identified 7,172 citations potentially addressing the key questions of interest to this evidence review. Of those, 2,857 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 4,315 abstracts were reviewed with 3,050 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a Key Question of interest to this review, did not enroll population of interest, or published prior to January 2007. A total of 1,265 full-length articles were reviewed. Of those, 884 were excluded at a first pass review for the following: not addressing a key question of interest (42%), not enrolling the population of interest (26%), not meeting the inclusion criteria for clinical study or systematic review (21%), or being a duplicate (11%). A total of 381 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 262 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 in the original guideline document.

Criteria for Study Inclusion/Exclusion

General Criteria

- Clinical studies or systematic reviews published on or after January 1, 2007 (eliminated via filtered search)
- Studies must have been published in English (eliminated via filtered search)
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence (partially eliminated via filtered search)
- Studies must have enrolled a patient population in which at least 85% of patients had CKD (stage 1, 2, 3, or 4) or associated condition or symptoms
- Studies enrolled adults 18 years or older; in studies that mixed adults and children, at least 85% of the enrolled patients had to be 18 years or older

Prevention, Pharmacologic Treatment, and Management Strategies

- Studies must have evaluated a treatment or management strategy for CKD
- Studies must have been a randomized controlled trial (RCT), prospective controlled clinical trial (CCT) or a systematic review of RCTs and/or CCTs. If no studies meet this criterion for all or part of a given key question, large observational studies (n ≥500 patients) will be considered for inclusion
- Crossover trials were considered only if data from the first treatment period were reported separately
- Studies must have enrolled ≥10 patients per treatment arm
- Studies must report data on at least one of the included outcomes
- Studies must have followed patients for at least 4 weeks; the exception is studies addressing Key Questions with acute kidney injury as an outcome (Key Question 1 and 2), which have no minimum follow-up time requirement
- All subjective outcomes (e.g., quality of life) must be measured using validated instruments

CKD Risk Factor Awareness Studies (Key Question 2)

- Studies must have been a case controlled or a comparative cohort study that assesses presence versus absence of occupational exposure (e.g., development of CKD in occupational exposure cohort versus cohort without exposure, or history of occupational exposure in patients with CKD versus comparison group without CKD)
- Studies must have investigated occupational exposures that may increase the risk of CKD. Expert opinion papers were not considered as evidence addressing this question

Literature Search Strategy

Name	Date Limits	Platform/Provider
Agency for Healthcare Research and Quality (AHRQ)	2007 through December 12, 2013	U.S. Department of Health & Human Services
Cochrane Library	2007 through December 4, 2013	John Wiley and Sons, Ltd.
EMBASE	2007 through December 2, 2013	OVID Technologies, Inc.
MEDLINE	2007 through December 2, 2013	OVID Technologies, Inc.
National Institute of Health and Care Excellence (NICE)	2007 through December 4, 2013	National Institute for Health and Care Excellence
PubMed (In-process, Publisher, and PubMedNotMedline records)	2007 through December 4, 2013	National Library of Medicine (NLM)

See Appendix A in original guideline document for a detailed list of search strategies for each key question.

Number of Source Documents

Overall, 115 studies addressed one or more of the Key Questions and were considered as evidence in this review. See Figure A-1 in the original guideline document for a systematic review flow diagram.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

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Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Abstracting and Managing Data

For each study included in the literature review, the following study level details were abstracted: country, purpose, and quality rating. For previous systematic reviews, team members reported the search strategy used, study selection criteria, and overall information about the evidence base,

including number of included studies and overall patients enrolled. For all studies, reviewers abstracted data about characteristics of the included patients and interventions being assessed.

Assessing Individual Studies' Methodological Quality (i.e., Internal Validity or Risk of Bias)

As per the Department of Veterans Affairs/Department of Defense (VA/DoD) *Guideline for Guidelines* document (see the "Availability of Companion Documents" field), risk-of-bias (or study quality) of individual studies and previous systematic reviews was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of Good, Fair, or Poor based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of Good, Fair, or Poor ratings for different study designs appear in Appendix VII of the USPSTF procedure manual.

Data Synthesis

A narrative approach to synthesizing the evidence for all the Key Questions was used. As indicated in the VA/DoD *Guideline for Guidelines* document, the first line of evidence was previous systematic reviews. For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. Reviewers considered whether subsequent evidence supports the conclusions reported in the previous review. For questions for which no previous review was available, the overall findings for the outcomes of interest of the studies that addressed a key question were summarized.

Assessing the Overall Quality of the Body of Evidence for an Outcome

The overall quality of the body of evidence supporting the findings for the outcomes of interest was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered.

The GRADE system rates the overall quality of the evidence as High, Moderate, Low, and Very Low (see the "Rating Scheme for the Strength of the Evidence" field). For instance, a body of evidence that consists of randomized controlled trials (RCTs) automatically starts with a rating of high quality. This rating can be downgraded if some of the RCTs have serious flaws such as lack of blinding of outcome assessors, not reporting concealment of allocation, or high dropout rate. Similarly, the quality can be downgraded or further downgraded if inconsistencies of findings are present or if there is a lack of precision surrounding an outcome's effect size. For more information on the GRADE system go to the GRADE working group website at the following link: http://www.gradeworkinggroup.org/.

Assessing Applicability

When describing the evidence base addressing a Key Question, the evidence review team discussed aspects of the included studies, such as characteristics of included patients and treatments being assessed that may make the overall findings of the studies more or less applicable to the population, treatments, or outcomes of interest to the review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The methodology used in developing the 2014 Clinical Practice Guideline (CPG) follows the *Guideline for Guidelines*, an internal document of the Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) (see the "Availability of Companion Documents" field). The current document is an update to the 2008 VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the development and submission of an updated Chronic Kidney Disease (CKD) CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by primary care providers within the VA/DoD health care system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management of patients with CKD. In addition, the Champions assisted in:

1. Providing direction on inclusion and exclusion criteria for the evidence review
2. Assessing the level and quality of the evidence
3. Identifying appropriate disciplines of individuals to be included as part of the Work Group
4. Directing and coordinating the Work Group
5. Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, US Army Medical Command, the proponent for CPGs for the DoD, identified three clinical leaders as Champions for the 2014 CPG.

The Lewin Team (Team), including DutyFirst Consulting, ECRI Institute and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The team held the first conference call in August 2013, with participation from the contracting officer's representatives (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of CKD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of CKD, from which Work Group members were recruited. The specialties and clinical areas of interest included: Clinical Dietetics, Geriatrics, Family Medicine, Internal Medicine, Nephrology, Nursing (including advance practice nursing), Pharmacy and Social Work.

The guideline development process for the 2014 CPG update consisted of the following steps:

1. Formulating evidence questions (Key Questions)
2. Conducting the systematic review
3. Convening a face-to-face meeting with the CPG Champions and Work Group members
4. Drafting and submitting a final CPG about the management of CKD to the VA/DoD EBPWG

Appendix A in the original guideline document provides a more detailed description of each of these tasks.

Reconciling 2008 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence or as scheduled subject to time-based expirations. For example, the U.S. Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services. Further, the inclusion criteria for the National Guideline Clearinghouse (NGC) specify that a guideline must have been developed, reviewed or revised with the past five years.

The CKD Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the Key Questions. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous 2008 CKD CPG, subject to evolving practice in today's environment. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. The wording was, however, modified slightly to be best utilized in today's clinical environment and to uphold the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendation format. For these modified recommendations, the Guideline Work Group referred to the available evidence as summarized in the body of the 2008 CKD CPG and did not assess the evidence review that was conducted for the 2008 CKD CPG. These "modified carryover" recommendations are noted in the recommendations list.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2008 CKD CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2008 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2008 CKD CPG as well as harms and benefits, values and preferences, and other implications, where possible. In some instances, peer-reviewed literature published since the 2008 CKD CPG was considered along with the evidence base used for that CPG. Where such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system, it is noted in the discussion that follows the corresponding recommendation.

The Guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and, therefore, may introduce bias.

Convening the Face-to-Face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on March 17-20, 2014. These experts were gathered to develop and draft the clinical recommendations for an update to the 2008 CKD CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2008 CKD CPG. The members also developed new clinical practice recommendations, not presented in the 2008 CKD CPG, based on the 2014 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

Following the drafting of clinical practice recommendations, the Work Group assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Refer to the original guideline document for further descriptions of each domain.

The framework in Table A-3 in the original guideline document was used by the Work group to guide discussions on each domain.

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low. In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2008 CKD CPG that would form the narrative text for the 2014 CKD CPG. During this time, the Champions also revised the 2008 algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the EBPWG following the publication of the 2014 CPG. The algorithms will be included as part of this CPG so as to provide a clear description of the flow of patient care. The final 2014 CKD CPG was submitted to the EBPWG in December 2014.

Rating Scheme for the Strength of the Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "The guideline panel recommends offering this option …")
- Weak For (or "The guideline panel suggests offering this option …")
- Weak Against (or "The guideline panel suggests not offering this option …")
- Strong Against (or "The guideline panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A thorough explanation of the guideline validation process and public comment is provided in the Department of Veterans Affairs and the Department of Defense (VA/DoD) *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Table A-2 in the original guideline documents indicates the number and type of studies that addressed each of the questions. The evidence base consists primarily of systematic reviews and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Formulation of an efficient and effective assessment of the patient's condition
- Optimizing the use of therapy to reduce symptoms and enhance functionality
- Minimizing preventable complications and morbidity

- Emphasizing the use of personalized, proactive, patient-driven care

Potential Harms

- In a systematic review of intravenous (IV) versus oral iron therapy, adverse effects were reported in 50% of included studies. The most common side effects reported for oral iron therapy were gastrointestinal-related; for IV iron therapy hypotensive and allergic reaction were the most common side effects. There was limited data on mortality, cardiovascular mortality and quality of life. For patients receiving IV iron therapy, some of the burdens would be increased costs; inconvenience of travel and time to an infusion center or clinic for treatment; risks associated with any IV therapy, such as venous infiltration; and potential serious adverse effects, such as anaphylaxis.
- Use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) will commonly increase serum creatinine and potassium. An increase up to 30% in serum creatinine within the first two weeks after initiation is acceptable. If potassium becomes elevated, measures to reduce hyperkalemia (e.g., reduction in dose of ACEI or ARB, discontinuation of concomitant medications that may increase potassium, implementation of a low potassium diet, addition of a diuretic, as indicated) should be considered.
- Patients with cough due to ACEI should be switched to an ARB. It is unknown if an ARB can be safely used as an alternative in patients who have previously developed angioedema on an ACEI. A systematic review found the risk for angioedema to be 9.4% (95% confidence interval [CI] 1.6 to 17%) of patients on an ARB who previously experienced angioedema on an ACEI; and 3.5% (95% CI 0 to 9.2%) of patients with previously confirmed angioedema on an ACEI. Another review estimated the risk of cross-reactivity of angioedema with an ARB in patients who previously experienced this adverse event with an ACEI to be from less than 7% up to 17%. Therefore, an ARB should be used with caution in patients who have previously experienced angioedema with an ACEI.
- Refer to Appendix B, "Pharmacotherapy with ACEIs or ARBs," in the original guideline for additional information on adverse effects of these medications.
- Refer to Table 2, "Select Medications Requiring Dose Adjustments or to be Used with Caution in Patients with CKD," in the original guideline document for additional information on medications to be used with caution.

Contraindications

Contraindications

- Kidney transplant patients receiving immunosuppressive drugs should not be administered live viral vaccines, such as varicella, zoster, (nasal) influenza and measles, mumps, rubella (MMR). These patients are at risk for developing disseminated viral infection due to immunosuppressive therapy.
- Live vaccines, including nasal influenza (live attenuated influenza virus [LAIV]), may be contraindicated in patients with chronic kidney disease (CKD) and severe immunodeficiency including treatment with immunosuppressive agents.
- Metformin is contraindicated in men with a serum creatinine greater than 1.5 mg/dL and in women with a serum creatinine greater than 1.4 mg/dL.
- Angiotensin-converting enzyme inhibitors (ACEIs) are contraindicated in patients with a history of angioedema on an ACEI.
- Due to the potential risk for fetal morbidity and mortality in patients taking an ACEI during pregnancy, it is recommended that therapy be discontinued as soon as a woman becomes pregnant; alternate therapy should be considered.

Qualifying Statements

Qualifying Statements

- The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.
- This Clinical Practice Guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.
- Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available

resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.
- These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Implementation of the Guideline

Description of Implementation Strategy

This Clinical Practice Guideline (CPG) and algorithm are designed to be adapted by individual health care providers with consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine the best interventions and timing of care for their patients in order to optimize quality and improved clinical outcomes.

Although this CPG represents the practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPGs may lead to the development of new practice-based evidence.

Implementation Tools

Clinical Algorithm

Patient Resources

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Management of Chronic Kidney Disease Working Group. VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 117 p. [171 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2000 Nov (revised 2014 Dec)

Guideline Developer(s)

Department of Defense - Federal Government Agency [U.S.]

Department of Veterans Affairs - Federal Government Agency [U.S.]

Veterans Health Administration - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Management of Chronic Kidney Disease Guideline Working Group

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Financial Disclosures/Conflicts of Interest

A hallmark of the Department of Veterans Affairs and the Department of Defense (VA/DoD) guidelines is their relative freedom from conflict of interest. Conflicts of interest faced by the VA/DoD Evidence-Based Practice Working Group (EBPWG) and the working groups that it charters to develop specific guidelines are handled based on the Veterans Health Administration (VHA) Handbook 1004.07 - Financial Relationships between VHA Health Care Professionals and Industry, which was signed October 21, 2009. All EBPWG meetings utilize the process of real-time verbal disclosure as required by VHA Handbook 1004.07 - Information for Members of VHA Decision Making and Advisory Groups.

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest in the past two years, including verbal affirmations of no conflict of interest at regular meetings. The project team was also subject to random web-based surveillance (e.g., ProPublica). If there was a positive (yes) conflict of interest response (actual or potential), then action was taken by the co-chairs and evidence-based practice program office, based on the level and extent of involvement to mitigate the conflict of interest. Actions ranged from restricting participation and/or voting on sections related to a conflict, to removal from the Work Group. Recusal was determined by the individual, co-chairs, and evidence-based practice office. No member of the final project team had any conflict of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for management of chronic kidney disease in primary care. Washington (DC): Department of Veteran Affairs, Department of Defense; 2007. 126 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Department of Veterans Affairs Web site.

Print copies: Available from the Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Availability of Companion Documents

The following are available:

- VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. Clinician summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 11 p. Electronic copies: Available from the Department of Veterans Affairs (VA) Web site.
- VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. Pocket card. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 6 p. Electronic copies: Available from the VA Web site.
- Guideline for guidelines. Washington (DC): Department of Veterans Affairs; 2013 Apr 10. Electronic copies: Available from the VA Web site.
- Putting clinical practice guidelines to work in VHA. Washington (DC): Department of Veterans Affairs. 64 p. Electronic copies: Available from the VA Web site.

In addition, a pharmacotherapy table is available in Appendix B of the original guideline document.

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Patient Resources

The following is available:

- VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. Patient summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 3 p. Electronic copies: Available from the Department of Veterans Affairs Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on August 9, 2002. The information was verified by the guideline developer on September 25, 2002. This summary was updated by ECRI on January 12, 2005 following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of some non-steroidal anti-inflammatory drug products. This summary was updated on April 15, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on June 22, 2010. This summary was updated by ECRI Institute on June 27, 2011 following the U.S. Food and Drug Administration advisory on Zocor (simvastatin). This summary was updated by ECRI Institute on July 15, 2011 following the U.S. Food and Drug Administration advisory on erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. This summary was updated by ECRI Institute on April 13, 2012 following the U.S. Food and Drug Administration advisories on Statin Drugs and Statins and HIV or Hepatitis C drugs. This summary was updated by ECRI Institute on February 4, 2015. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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